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LETTERS TO THE EDITOR

AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE

Dear Editor:

The health implications of environmental tobacco smoke (ETS) remain controversial. Neither the published reports nor statements from public health officials and agencies have resolved the question of ETS health effects, nor are they likely to in the near future.

A. Judson Wells' paper, "Estimate of Adult Mortality in the United States from Passive Smoking" (1988) is yet another effort to draw scientific verity from a reassessment of published epidemiological data. But this new look does not change the quality or meaning of the existing evidence, which remains equivocal. Neither does it substantively support the author's statement that exposure to ETS "can have adverse long term health effects that are more serious than previously thought".

The conclusions of nonsmokers' increased risk of lung cancer from ETS exposure found in the reports of the National Academy of Sciences (NRC 1986) and of the Surgeon General (USSG 1986) were based on epidemiological studies that produced a wide range of findings. The relative risk (RR) values summarized in Table 12.4 of the NAS report ranged from 0.50 to 3.25, with 17 out of 20 risk estimates (for subgroups by sex) lacking statistical significance. In seven additional reports since the NAS document was published, relative risk values ranged from "<1.00" to 1.65, with only the latter being statistically significant. The RR values from all 29 subgroups in the 20 studies included in the NAS report plus those published later are summarized in Table 1 herein.

All of the epidemiological studies that comprise the data base for estimating nonsmokers' risk of lung cancer in relation to ETS are actually estimates of association based on spousal smoking. In not a single study was either exposure to ETS or retained dosage determined. A few studies have attempted to estimate the degree of exposure to spousal smoking in terms of hours per day or total years of exposure, but none of the studies measured ETS exposure in objective and quantitative terms or even estimated ETS exposure with any degree of reliability. Proximity to a smoker sitting across the dining table does not permit an estimate of the nonsmoker's exposure to ETS, which will vary according to room volume, ventilation rates, the physical and chemical changes in ETS as it ages, and other factors that influence the concentrations and duration of ETS exposure. A spouse's smoking in another room or in another building can have even less or no significance at all in assessing the possible role of passive smoking on a subject's health.

It should be recognized, also, that association can never establish causality. At best, association can only suggest the possibility of causality. Feinstein (1988), discussing public alarms based on epidemiological studies, recently pointed out that "a causal suspicion is supported if an impressive statistical association appears in the 2 by 2 tabulation for subgroups of people reported as being exposed or nonexposed, diseased or nondiseased".

There are many ways to look at data and try to draw meaning from the aggregation of values. After deciding that the 13 studies which survived critical assessment did not, individually or collectively, support a definitive conclusion on the risk of lung cancer in relation to spousal smoking, the NAS Committee performed a meta analysis on the aggregated data, leading to an estimated risk increase of about 34% for nonsmokers married to smokers. This estimate has been questioned on a variety of grounds by a number of investigators (Letzel et al. 1988).

It can be argued that even if a first order relationship does not exist between disease and passive smoking in the epidemiological studies, the data used by Wells are the best evidence available. And it can be argued that even the array of values shown in Table 1 is not impressive in the sense that Feinstein specifies, there are other ways of testing the data, as has been done by Wells.

Table 1. Statistical significance of risk values for lung cancer in relation to spousal smoking.

Investigator	Not Statistically Significant		Statistically Significant	
	Male	Female	Male	Female
*Chan and Fung (1982)		0.75		
*Buffler et al. (1984)	0.50	0.78		
Dalager et al. (1986)	<1.00			
*Kabat and Wynder (1984)	1.00	0.79		
Gao et al. (1987)		0.9 [a]		
*Gillis et al. (1984)		1.00		
*Lee et al. (1986)		1.00		
Gao et al. (1987)		1.1 [b]		
Shimizu et al. (1988)		1.1		
*Garfinkel (1981)		1.17[c]		
*Pershagen et al. (1987)		1.20		
Wu et al. (1985)		1.20		
*Lee et al. (1986)	1.30			
*Garfinkel et al. (1985)		1.31[c]		
*Akiba et al. (1986)	1.80	1.50		
*Koo et al. (1984)		1.64		
Brownson et al. (1987)		1.68		
Humble et al. (1987)	>1.20	1.80		
*Correa et al. (1983)	2.00	2.07[c]		
*Hirayama (1981)			2.25	1.63
Lam et al. (1987)				1.65
*Trichopoulos et al. (1981)				2.11
*Gillis et al. (1984)		3.25		

* Risk values from Table 12.4, National Academy of Sciences Report (1986)
a Exposure in adult life.
b Exposure in childhood.
c Statistically significant trends in one or more data subsets within the study.

There remains, however, the fundamental question of the quality of the individual underlying studies whose data are under consideration. Many of the epidemiological studies assessing the risk of lung cancer from spousal smoking have been criticized for a variety of methodological flaws and weaknesses, especially with regard to the potential for misclassification (Überla 1987; Balter et al. 1986; Lebowitz 1986; OTA 1986).

Misclassification of subjects is a source of error where patients claiming to be never smokers are in fact current or exsmokers. Wells conceded the likelihood of 5% misclassification. But misclassification of smoker status has been found at levels from 10% to 40% (Schwartz et al. 1988; Weiss 1988). NAS noted the likelihood of misclassification and lowered its estimate of the elevated risk to 25% from 34%, but it failed to indicate whether the lower value was statistically significant. (NAS found the combined risk from American studies a 14% increase, which was not statistically significant.)

Misclassification of disease can also be a source of error. There was a marked potential for misclassified disease in the studies having statistically significant risk ratios in the NAS and Surgeon General's reports. In Hirayama's study of Japanese women, his 1984 report suggests that only 21 of the 200 lung cancer cases (10.5%) were histologically confirmed, while the Surgeon General's report states that "none" were verified. Akiba et al. (1986) studying survivors of the Hiroshima and Nagasaki atom bombings, noted 43% of the lung cancer cases had not been histologically confirmed. Weiss (1988) notes that "thirteen percent of the cases [in Garfinkel's study] proved on review not to involve lung cancer".

Misclassification of exposure can be a source of uncertainty in studies that attempt to find exposure-response relationships. There is little basis for considering estimates of spouses' smoking to be reliable. Pron et al. (1988) concluded that "test-retest estimates of reliability [over a six-month time span] would suggest that misclassification of such exposures may be extensive". Vogt (1977) found "twenty-two percent of persons gave different answers on the two questionnaires [on the number of cigarettes smoked per day] given about an hour apart".

Among the variety of flaws and weaknesses found in the various epidemiological studies on ETS and lung cancer, it is worth noting the age bias found by Ahlborn and Überla (1988) in Hirayama's study and their conclusion that "the risk increase ... disappears completely when one removes selection bias by age". Überla (1987), highlighting the weaknesses of the epidemiological studies comprising the NAS data base, had earlier concluded, "False plus false does not equal true."

In addition, most of the epidemiological studies have failed to take into account significant confounding factors in assessing lung cancer risk in relation to ETS. Many risk factors for lung cancer have been identified, including exposure to heavy metals, organic chemicals, combustion by-products, natural and man-made radiation, diet, and nutritional status, personal health history, emotional, and psychological factors. Holst et al. (1988) recently reported significantly increased risk in relation to keeping pet birds and to reduced vitamin C intake. Gao et al. (1987) found no significant increased risk for Chinese women in relation to passive smoking or type of employment but did find significantly increased risk in relation to previous lung disease, cooking practices, and shorter menstrual cycles, reflecting hormonal factors. Some of these factors may act independently, but many may interact. Any attempt to assess the role of one factor must take into account all other relevant factors.

None of the epidemiological studies on spousal smoking took into account confounding factors other than attempting to match cases with controls by age, residence, and general socio-economic status. Of the 20 epidemiological studies, those by Hirayama and by Lam et al. (1987) have the two largest number of lung cancer cases, with the increased risk in both being statistically significant. Both studies are of Oriental populations, which suggests that many factors like cooking practices and fuels for cooking and heating should have been controlled.

All of the studies included in Wells' Table 4, on which he based his estimate of heart disease deaths related to passive smoking, similarly fail to consider the confounding effect of the many cardiovascular disease risk factors that have already been established for that disease.

Some observers have commented that increased risk of lung cancer from ETS exposure seems implausible because the ETS components are so dilute in ambient air compared to the concentrations of these substances in mainstream smoke. In addition, it has been found that nonsmokers retain far less of inhaled ETS than active smokers retain of mainstream smoke. Wells noted that "smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day". This is more than one order of magnitude greater than Rickert's calculation (1988) that nonsmokers exposed to ETS retain about 1/8000 the amount of particulate matter retained by the active smoker. Lee (1988) cited estimates of the same range: 1/5000 for males, 1/10 000 for females. All of these estimates are probably on the high side, since none of the studies appears to have considered the chemical and physical changes that occur as ETS ages and the losses of ETS through evaporation, fallout, and deposition over time.

Other observers have commented on the implausibility that lung cancer in nonsmokers might be caused by ETS. Aviado (1988) noted that none of 17 constituents of ETS "designated as suspect carcinogens ... [has] been adequately shown to cause pulmonary cancer via inhalation in animals". Crawford (1988) noted that "no atypical cellular changes have been found in the lungs of nonsmokers". Lee (1987) concluded "that exposure to smoke constituents of nonsmokers is too low to explain the moderate increase in risk of lung cancer seen in epidemiological studies in self-reported never smokers married to smokers. This increase in risk is much more plausibly explained by misclassification of smokers as nonsmokers than by a direct effect of passive smoking".

Wells has attempted to make his calculation of annual deaths from exposure to ETS appear more reasonable by comparing it to the larger estimate of Repace and Lowrey, but their estimate has been severely criticized because the controls were Seventh Day Adventists (SDA) whose life style is so radically different from that of the non-SDAs married to smokers that the comparison is considered inappropriate (OTA 1985; Balter et al. 1986; Überla 1987).

Taking these and other factors into account, Gostomzyk (1986) concluded, following the International Experimental Toxicology Symposium on Passive Smoking in Essen, FRG, that "even toxicology has not been able to ascertain with any greater degree

of probability than did epidemiology that there exists a link between damage to health and passive smoking".

Perhaps it is the weight of these facts, interpretations, and opinions that caused no less an authority than the American Cancer Society to assert last year that "the currently available evidence is not sufficient to conclude that passive or involuntary smoking causes lung cancer in nonsmokers..." (ACS 1988).

A final comment: both the title and the content of the editorial that accompanied the Wells paper suggests that the paper provides stronger evidence of risk of cardiovascular disease (CVD) for nonsmokers married to smokers than the paper in fact offers. In 1986, both the NAS and USSG reports noted the lack of convincing evidence of significant CVD risk from ETS exposure. More recently, Fielding and Phenow (1988) commented on papers reporting an association between ETS exposure and CVD risk, concluding that "no firm conclusion that a causal relation exists is yet warranted".

Wells' calculations with respect to CVD are based on data from epidemiological studies that have the same weaknesses as the lung cancer studies. There is, thus, no basis for greater confidence in his estimate of heart disease deaths in relation to ETS than his estimate of lung cancer deaths.

It is commendable that those who are not satisfied continue to seek more meaning from the data. But in an issue as serious as this, it is important to note when the data fail to meet the standards for scientific inference.

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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING; A RESPONSE

Dear Editor:

Wells (1988) estimates that exposure to environmental tobacco smoke (ETS) causes 46 000 deaths per year in the U.S.; 3000 from lung cancer, 11 000 from other cancers, and 32 000 from heart disease. These estimates are scientifically unjustified. Far too much faith is placed on results from often fragile epidemiological studies, with major sources of bias ignored or totally underestimated. In contrast, far too little faith is placed on evidence that nonsmokers have very much lower exposure to tobacco smoke constituents than do smokers, and that smokers are much more exposed to ETS than nonsmokers.

The evidence that exposure to ETS increases the risk of developing heart disease is extremely unconvincing. Of the studies cited by Wells, some are based on unacceptably small numbers of cases, e.g., Garland et al. (1985) where only two deaths occurred in women married to never-smoking husbands, while the only two studies with substantial numbers of deaths are both open to question.

When referencing the Japanese prospective study, Wells uses Hirayama's 1984 report of a statistically significant positive trend in wife's age-adjusted risk according to husband's smoking, but does not comment on the fact that, in 1981, Hirayama reported no association whatsoever. As shown in Table 1, the

Table 1. Female relative risks for heart disease from passive smoking in Japanese study.

Follow-up period	Total cases	Husband's smoking habit		
		Non-smoker	Ex or <19/day	20+/day
1966-79	406	1	0.97	1.03
1980-82[1]	88	1	2.85	5.07
1966-82	494	1	1.10	1.30

[1] Estimated from 1966-79 data (Hirayama 1981) and from 1966-82 data (Hirayama 1984). The 1984 paper provided relative numbers of deaths as 118, 240, and 136.